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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/836,145	CRAVATT ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 July 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☒ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: 12,14,16-18 and 20-24.

   Claim(s) withdrawn from consideration: 1-11, 13, 15 and 19.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: Please see attached sheet

The After-Final amendment is denied entry for the following reasons:

1. Claim 25 sets forth new claim limitations (e.g., "wherein heterocyclic is selected from a group consisting of pyridyl ... and aziridine"), which introduces new search and consideration and the issue of new matter.

2. There is no reason given for why the amendment was not earlier presented.

In order to expedite the future prosecution of the present application the following comments are noted:

Claim Rejections - 35 USC § 112 – Written Description

Argument/Response

3. Applicant's arguments (i.e., see 7/12/04 After Final Amendment) directed to the written description rejection (i.e., see 4/7/04 Final Rejection) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons.

[1] Applicants argue that they have provided "a representative number of species" to show that they were in possession of the claimed invention and cite *In re Bell* in support of this position (e.g., see 7/12/04 Response, page 7-8, especially page 8 wherein Applicants quote various portions of the specification that allegedly provide support an adequate written description of the claimed invention).

[2] Applicants state that the Examiner mistakenly asserted that only one "non-directed" library of "activity based probes" is disclosed in the specification and cite various passages in the specification in support of this position (e.g., see 7/12/04 Response, pages 8-10).

This is not found persuasive for the following reasons:

[1] The Examiner contends that *In re Bell* does not apply here because the art is unpredictable. The Examiner agrees with Applicants that an "adequate description of a 'representative number' of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces" (see MPEP § 2163). However, the Examiner notes that *In re Bell* requires an "unsupported" list of species to be in a "predictable" art area (e.g., see MPEP § 2163, "in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species. Cf. *In re Bell*, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed.Cir. 1993)"). Here, no such "genetic code" or other distinguishing feature and/or formula (e.g., structure/function relationship) exist that would allow a person of skill in the art to conclude that Applicants were in possession of the claimed invention. Although Applicants refer to the examples in the specification and state, "In view of the foregoing [examples], it is submitted that it cannot be reasonably maintained that the specification contains no "distinguishing structural attributes" for the moieties 'X' and 'R" (e.g., see 7/12/04 Response, page 8, middle paragraph), the Examiner

notes that Applicants never state what those "distinguishing structural attributes" are? The only common structural features (e.g., see 7/12/04 Response, wherein Applicants quote paragraph 86 on page 21) that are shared by the list of compounds/chemical groups cited by Applicants are that they all contain carbon atoms. Clearly, the mere fact that a compound possesses a carbon atom would not reasonably lead a person of skill in the art to any particular active site probe/chemical group because all organic molecules posses a carbon atom and clearly not all organic molecules would function in this manner.

However, even if *assuming arguendo* that *In re Bell* does apply the Examiner contends that the disclosed species do not "adequately" describe the full scope of the claimed invention. Factors to be considered in determining whether there is sufficient evidence of possession include "(1) the level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention" (e.g., see MPEP § 2163). The Examiner contends (1) that the level of skill and knowledge in the art is low because the prior art is in its infancy (e.g., see Adam et al. wherein Applicants admit that they cannot generalize their one working example to the infinite number of compounds that are currently being claimed; see also original rejection wherein this reference was discussed at length), (2-3) Applicants have put forth no structural limitations or physical and/or chemical properties that would allow a person of skill in the art to narrow the number of possibilities that would need to be screened by Applicants method, (4) the functional characteristics are NOT coupled with a known or disclosed correlation between structure and function and (5) Applicants have provided only ONE example for making activity based probes wherein F = $-SO_3-$; L = N-

(5-penylamine)-decanamido; X is biotin and R represents small alkyl, aromatic and heteroaromatic groups and, as a result, Applicants list of potential species in the specification does not remedy this deficiency. Furthermore, Applicants have not provided any general methodology for synthesizing the infinite number of R(F-L)-X activity based probes that are currently claimed.

[2] The Examiner respectfully disagrees. The quoted passages in the specification represent a mere "laundry list" or "wish list" of potential compounds/groups that "might" work and thus do not constitute actual working examples (e.g., See, *Fujikawa v. Wattanasin*, 93 F.3d 1559,1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

In addition, the Examiner notes that ***Applicants have again failed to address the Adams et al. reference*** which clearly demonstrates that Applicants were not in possession of the claimed invention because the reference explicitly states that the compounds in Applicants' specification (i.e., the "laundry list" or "wish list" referred to by Applicants) have not been tested (e.g., see Adam, G. C.; Cravatt, B. F.; Sorensen, E. J. "Profiling the specific reactivity of the proteome with non-directed activity-based probes" Chemistry & Biology 2001, 8, 81-95, especially conclusion on page 91, column 1, paragraph 1, "Finally, the discovery that sulfonate probes not only labeled cALDH-I in complex proteomes, but also inhibited this enzyme's catalytic activity suggests that, at least in this one example [i.e., Applicants make no promise that it will work for any other examples], a screen for heat-sensitive labeling events accurately identified a small molecule-protein reaction that impacted the protein's biological function. **If** this correlation

proves generalizable [i.e., the correlation may NOT prove generalizable since Applicants use the word "If"], non-directed approaches for profiling the specific reactivity of the proteome may [or may not] generate chemical reagents applicable for both proteomics investigations and cell-based functional screenings"). Here, Applicants admit that they cannot "generalize" their only working example to the infinite number of possibilities that are currently being claimed (or listed in the specification). Their admission clearly demonstrates that Applicants claimed scope represents a mere "wish" or "plan" which does not satisfy the written description requirement (e.g., see *Fiers v. Revel* wherein the Court stated that an adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself").

Accordingly, the written description rejection is hereby maintained.

Claim Rejections - 35 USC § 112 - Enablement

Argument/Response

4. Applicant's arguments (i.e., see 7/12/04 After Final Amendment) directed to the Enablement rejection (i.e., see 4/7/04 Final Rejection) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons.

[1] Applicants again argue that they have provided enough guidance by citing several "laundry lists" or "wish lists" in the specification of potential chemical groups and/or enzymes that "might" be used in the presently claimed invention (e.g., see 7/12/04 Response, pages 11-12). Applicants also state that one working example is enough to enable the full scope of the claims and cite *In re Fisher* in support of this position (e.g., see 7/12/04 Response, page 13).

[2] Applicants argue that the specification provides instruction on "how to select an appropriate functional group for protein target" and cite paragraph 102 on page 27 of the original specification in support of this position (e.g., see cited paragraph on bottom of page 12 of 7/12/04 Response, which states that a "chemically reactive group is a moiety including a reactive functionality that does not react efficiently with the generally available functional groups of proteins ... but will react with a functionality present in a particular conformation on the surface [etc.]").

This is not found persuasive for the following reasons:

[1] First, the Examiner contends that the test for Enablement has been set forth by the CAFC in the *In re Wands* case (e.g., see 4/7/04 Final Rejection, page 13, paragraph 10 wherein "8" Wands factors were set forth e.g., breadth of claims, nature of invention, state of prior art, etc.). Here, Applicants have not addressed any of the "Wands" factors and thus have conceded the Enablement argument with regard to this test. For example, the Examiner stated in a previous office action that Applicants claimed invention reads on an infinite number of possibilities and, as a result, the breadth of the claims is enormous (i.e., refers to Wands factor #1). Again, the Examiner notes that Applicants have never refuted this position (i.e., Applicants concede this Wands factor) wherein the Examiner previously stated that the fact that the

specification describes "well-defined" activity based probes has no bearing on the number of probes that are being set forth in the claims (i.e., you can have an infinite number of "well-defined" probes). In addition, the Examiner previously noted the enormous number of R(F-L)-X probes generated by substituting the groups mentioned by Applicants citations (e.g., see 1/12/2004 Response, pages 21-22) would be astronomical because each position (e.g., R, F, L and X) can be varied independently. These statements were never refuted. Likewise, the other Wands factors have also been conceded.

With regard to Applicants' cited passages, the Examiner contends that the specification only provides "general" guidance, which is insufficient to provide adequate support in an unpredictable art area (e.g., see MPEP § 2163, "In contrast, for inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession"). Here, none of Applicants cited passages provide guidance with respect to ***specific*** R(F-L)-X activity based probes in use with a ***specific*** target proteins (other than the cALDH-I example). Thus, only general lists of "potential" candidates are disclosed.

While it is true that working examples are not required, it is often necessary to provide description and enablement for broad claims (e.g., see MPEP § 2164.02 wherein working examples are set forth as factors to be considered, especially in a case involving an unpredictable and undeveloped art). Thus, in applications directed to invention in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). Here, Applicants admit that the art is "unpredictable" (e.g., see Adam, G. C.; Cravatt, B. F.; Sorensen,

E. J. "Profiling the specific reactivity of the proteome with non-directed activity-based probes" Chemistry & Biology 2001, 8, 81-95, especially conclusion on page 91, column 1, paragraph 1, "Finally, the discovery that sulfonate probes not only labeled cALDH-I in complex proteomes, but also inhibited this enzyme's catalytic activity suggests that, at least in this one example [i.e., Applicants make no promise that it will work for any other examples i.e., they cannot "predict" what will happen], a screen for heat-sensitive labeling events accurately identified a small molecule-protein reaction that impacted the protein's biological function. If this correlation proves generalizable [i.e., the correlation may NOT prove generalizable i.e., Applicants use the word "If"], non-directed approaches for profiling the specific reactivity of the proteome may [or may not] generate chemical reagents applicable for both proteomics investigations and cell-based functional screenings"). Thus, Applicants admit that they cannot "generalize" their only working example of an eleven membered sulfonate ester library to the infinite number of possibilities that are currently claimed (or presented as a "wish" list in the specification) by explicitly stating that a correlation has not yet been established. Finally, the Examiner also notes that ***Applicants have failed again to address the Adam et al. reference*** set forth above, which explicitly states that the compounds/groups listed in the specification have not yet been tested.

[2] The Examiner contends that the cited passage represents a functional definition for a chemically reactive group that provides no guidance whatsoever for determining the identity of the chemically reactive compound/group because the definition only provides for a "desired outcome" (i.e., that ability to react with functionality present in a particular conformation n a surface), but does not set forth any means for determining what compounds/groups would provide such an outcome.

Accordingly, the Enablement rejection is hereby maintained.

Claims Rejections - 35 U.S.C. 102

Arguments/Response

5. Applicant's arguments (i.e., see 7/12/04 After Final Amendment) directed to 35 U.S.C. § 102 rejection (i.e., see 4/7/04 Final Rejection) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons.

[1] Applicants argue, "Purohit et al. fail to teach using a combinatorial chemical library which includes a plurality of compounds (e.g., see 7/12/04 Response, page 13, section C).

[2] Applicants argue, "While using any of compounds (1)-(6) shown by Figure 1 of the reference ... is disclosed by Purohit et al., using more than one of them simultaneously is not" (e.g., see 7/12/04 Response, paragraph bridging pages 13-14).

[3] Applicants argue, "while the present invention allows profiling classes of proteins in a sample on the basis of changes in protein activity rather than simply variations in protein level ... Purohit et al. merely teaches protein inhibition but does not provide for differentiating a complex mixture of proteins on the basis of activity" (e.g., see 7/12/04 Response, page 14, second paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. Compounds 4-6 in figure 1 of the Purohit et al. reference, for example, represent a combinatorial library with a "plurality" of compounds (i.e., at least three different compounds).

[2] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "using more than one of them [i.e., library members] simultaneously" i.e., "parallel" screening as opposed to "sequential" screening) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, Applicants arguments are not commensurate in scope with the claims.

[3] The Examiner respectfully disagrees. Purohit et al. do disclose "activity" based differentiation (e.g., see above rejection, "In addition, Purohit et al discloses isolating said conjugates from the active and inactive complex mixture (see Purohit et al, page 11509, column 2, paragraph 1). Finally, Purohit et al discloses comparing both "**active**" and "**inactive**" reaction mixtures (see Purohit et al, abstract, "The enzyme [sulfatase] is protected from inactivation by estrone sulfate [i.e., active form], which is also consistent with active site-directed inhibition. EMATE is proposed to inactivate estrone sulfatase by irreversible sulfamoylation of the enzyme [i.e., inactive form]"; see also page 11512, figure 6). Furthermore, Purohit et al discloses using two separate "portions" for the active and inactive mixture i.e., a "portion" with estrone sulfate added and a "portion" without any estrone sulfate added (see Purohit et al, page 11510, column 1, paragraph 1)". Thus, Purohit et al. is able to differentiate the complex mixture on the basis of activity (e.g., see also 11510, Results, "Nature of EMATE Inhibition of Sulfatase Activity" section, especially column 2, paragraph 4 wherein library members with different "on rates" are disclosed).

Accordingly, the 35 U.S.C. § 102 rejection is hereby maintained.

Claim Rejections - 35 USC § 103

Arguments/Response

6. Applicant's arguments (i.e., see 7/12/04 After Final Amendment) directed to the above 35 U.S.C. § 103(a) rejection (i.e., see 4/7/04 Final Rejection) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons.

[1] Applicants argue Gygi et al. fail to teach a "combinatorial chemical library comprising a plurality of members of the formula R*(F-L)-X" recited in claims 12 and 14 and that Liu et al. and Bogyo et al. fail to cure this deficiency (e.g., see 7/12/04 Response, page 14, last paragraph).

[2] Applicants argue that the presently claimed invention claims probes that "react with an active site of a protein", which Gygi et al. fails to show (e.g., see 7/12/04 Response, page 15, first paragraph).

[3] Applicants again submit that the Liu et al. reference is not available as prior art since the subject matter was derived from Applicants' own work as shown by the 37 C.F.R. 1.132 declaration submitted by Benjamin Cravatt on 1/12/2004 because "the proper rejection here can be based only on 'by others' clause of 102(a), and the Cravatt/Petricelli entity is not 'others' vis-a-vis the Cravatt/Petricelli/Sorensen/Adam entity" (e.g., see 7/12/04 Response, pages 15-17, especially page 17, second to last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. For example, Gygi et al. teach a "library" of ICAT reagents (i.e., heavy and light molecules) that are used to analyze complex protein

mixtures. In addition, the combined references of Liu et al. and Bogyo et al. teach that these ICAT reagents can be replaced with biotinylated sulfone probes that possess the requisite R*(F-L)-X formula. Consequently, the "combined" references do teach a combinatorial chemical library comprising members of the formula R*(F-L)-X because Gygi et al. teach the use of a "library" and Liu et al. and Bogyo et al. teach the use of R*(F-L)-X compounds. Please note that the term "library" has been broadly interpreted as any collection of two or more compounds (i.e., light and heavy compounds in this case). Please also note that nothing in Applicants' claims disclaims treating two separate samples with a library of reagents that are then subsequently combined as shown in figure 2 of Gygi et al.

[2] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "active site of a protein") is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

[3] The Examiner respectfully disagrees. "By others" is defined as "Any Combination of Authors or Inventors Different Than the Inventive Entity" (e.g., see MPEP § 2132, section III). Here, the Cravatt/Petricelli combination differs from the Cravatt/Petricelli/Sorensen/Adam/[Lovato] inventive entity by "two" inventors (i.e., Sorensen/Adam; please also note that "Lovato" has been mistakenly left out of Applicants' analysis and thus the actual difference here is "three" inventors). Thus, a combination of authors has been established that differs from the inventive entity. In addition, the Examiner notes that Cravatt's declaration never states that the Liu et al. reference is derived from the work of

Sorensen, Adam or Lovato [or even Petricelli]. It also contains several factual mistakes with regard to the prosecution history. For example, the 377 C.F.R. § 1.132 declaration mistakenly refers to Patent Application Serial No. 09/738,954. However, Patent Application Serial No. 09/738,954 is not under examination here (emphasis added). Therefore, the declaration is defective and, as a result, inadequate for the purpose of removing the Liu et al. reference.

Accordingly, the 35 U.S.C. § 103(a) rejection is hereby maintained.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
August 26, 2004

BENNETT CELSA
PRIMARY EXAMINER